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| (54) Title: 2-SUBSTITUTED 1,25-DIHYDROXYVITAMIN D ₃ DERIVATIVES (57) Abstract Vitamin D ₃ analogues which include a 2-substituted alcohol or fluoride are described. The preferred alcohol substituent is exemplified by the structural formula $-(CH_2)_4OH$ and the preferred fluoride substituents by the structural formulas $-(CH_2)_3F$ and $-(CH_2)_4F$. Methods for the preparation of a vitamin D ₃ analogue which includes a 2-substituted alcohol or fluoride starting with 2+4-cycloaddition of commercially available methyl 2-pyrone-3-carboxylate are also described. | | |

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2-SUBSTITUTED 1,25-DIHYDROXYVITAMIN D₃ DERIVATIVES**BACKGROUND OF THE INVENTION**

The present invention relates to novel
5 biologically active vitamin D₃ analogues which
include an alcohol or fluoride substituent in the
2-position and methods for their preparation.

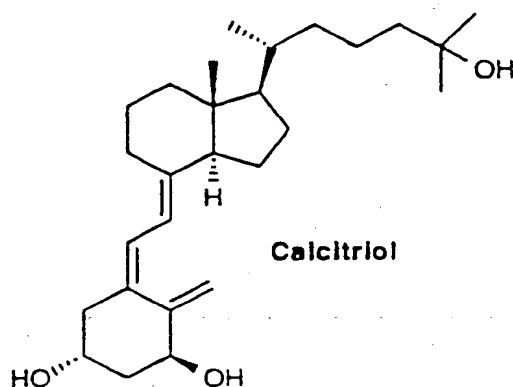
FIELD OF THE INVENTION

Vitamin D₃ analogues have been recognized as
10 having important biological activities. It is
known, for example, that vitamin D₃ analogues can
be used to control calcium and phosphate
metabolism.

It is also known that such analogues are
15 useful for inducing cell differentiation and for
inhibiting undesired cell proliferation. For
example, it is well recognized that vitamin D₃
produces 1 α ,25-dihydroxyvitamin D₃ (calcitriol)
during normal metabolism. Calcitriol is a potent
20 regulator of cell differentiation and
proliferation as well as intestinal calcium and
phosphorus absorption and bone calcium
mobilization. Calcitriol is also known to affect

the immune system and this compound, as well as a variety of synthetic vitamin D₃ derivatives have been used in practical, clinical chemotherapy of such diverse human illnesses as osteoporosis, cancer, immunodeficiency syndromes and skin disorders such as dermatitis and psoriasis. However, major research efforts are underway in an effort to prepare vitamin D₃ analogues as drugs in which calcitropic activity is effectively separated from cell growth regulation.

Calcitriol may be structurally represented as follows:



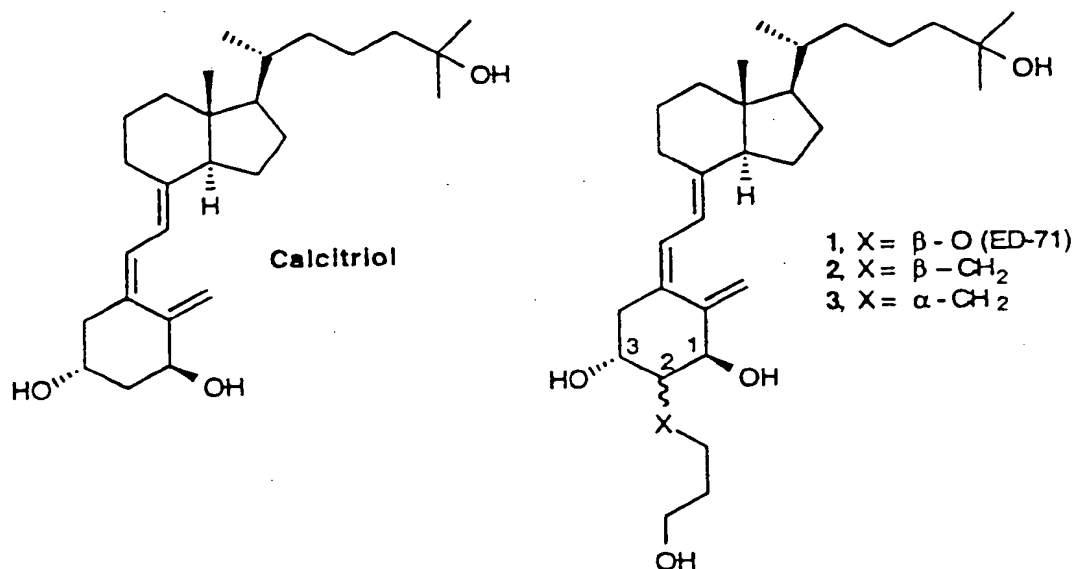
The upper and lower ring portions of calcitriol may be called, for ease of reference, the C/D-ring and A-ring, respectively.

DESCRIPTION OF THE RELATED ART

Especially for post-menopausal women, osteoporosis is a very serious illness that causes physical deformity and high susceptibility to bone (e.g., hip) fractures. In the general population aged above 65 years, osteoporosis ranks third to heart disease and cancer in terms of prevalence¹. It is estimated that 30% of women at 75 years and 40% of women at 85 years have abnormal bone loss². Calcitriol is being used, especially in Japan where dietary intake of calcium is low, for treatment of osteoporosis³. The Chugai Pharmaceutical Company has developed ED-71 (1) as a synthetic derivative of calcitriol, having a better therapeutic index than calcitriol⁴. This 2B-(3'-hydroxypropyloxy)-calcitriol has a two-fold stronger binding affinity to the rat plasma vitamin D-binding protein (DBP) than does calcitriol, suggesting that it circulates in the plasma with a longer half-life than calcitriol⁴. Furthermore, in animal models with osteoporosis, ED-71(1) is more effective than calcitriol⁴.

To probe structure-medicinal activity relationships in the hope of preparing a new osteoporosis drug with an even better therapeutic index than ED-71(1), we targeted the 2-carba-analogues 2 and 3, structurally represented below.

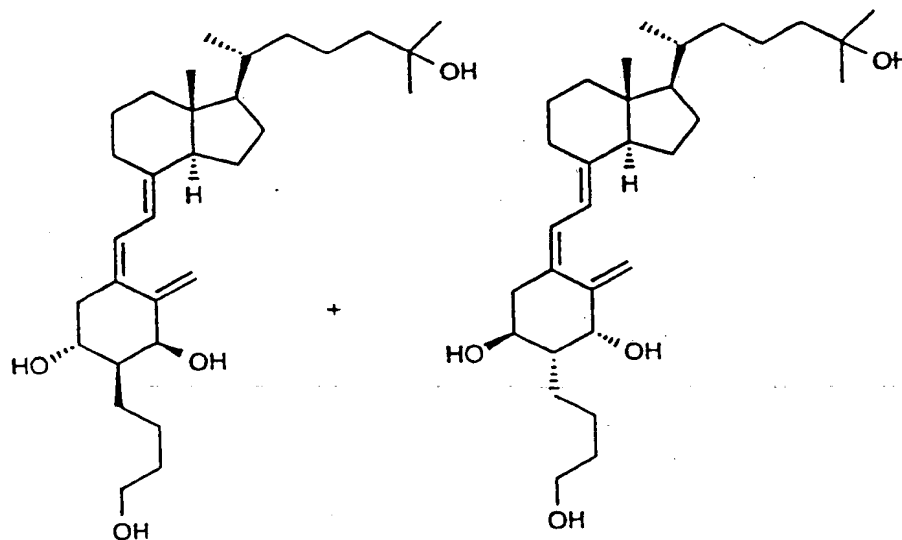
These analogues were chosen because replacing one oxygen atom by a methylene group, a relatively small change in a large steroid molecule, was anticipated, based on the current working model for receptor binding of ED-71(1)⁴, not to interfere with such critical receptor binding. also, these analogues were chosen for chemical reasons, probing whether recently developed Diels-Alder methodology⁵ using 2-pyrones and monosubstituted alkenes could be extended to 1,2-disubstituted alkene dienophiles with reliable and faithful transfer of olefin geometry ultimately into the stereochemical relationships at the 1- and 2-positions of the steroid targets. We record here the results of these chemical explorations and biological evaluations.



SUMMARY OF THE INVENTION

The present invention is for a vitamin D₃ analogue which includes a 2-substituted alcohol or fluoride. The preferred alcohol substituent is exemplified by the structural formula $-(CH_2)_4OH$ and the preferred fluoride substituents by the structural formulas $-(CH_2)_3F$ and $-(CH_2)_4F$.

The preferred diastereomers of the 2-substituted $-(CH_2)_4OH$ are represented by the following structural formulas:



The present invention is also for the related method of preparation of a vitamin D₃ analogue which includes a 2-substituted alcohol or fluoride starting with 2+4-cycloaddition of commercially available methyl 2-pyrone-3-carboxylate.

Diastereomeric 2-substituted calcitriol analogues were prepared in only eleven chemical operations, starting with 2+4-cycloaddition of commercially available methyl

5 2-pyrone-3-carboxylate. Highlights of this convergent and stereo controlled synthetic approach are as follows: (1) retention of reactant dienophile geometry in the product bicyclic lactone, characteristic of a concerted

10 inverse-electron-demand Diels-Alder cycloaddition; (2) an improved decarboxylation procedure involving chemospecific allyloxide opening of a lactone ring in the presence of a methyl ester and then non-high pressure palladium-promoted allylic

15 ester decarboxylation; and (3) use of the enantiomerically pure C,D-ring chiron 14 to resolve racemic A-ring phosphine oxide 13.

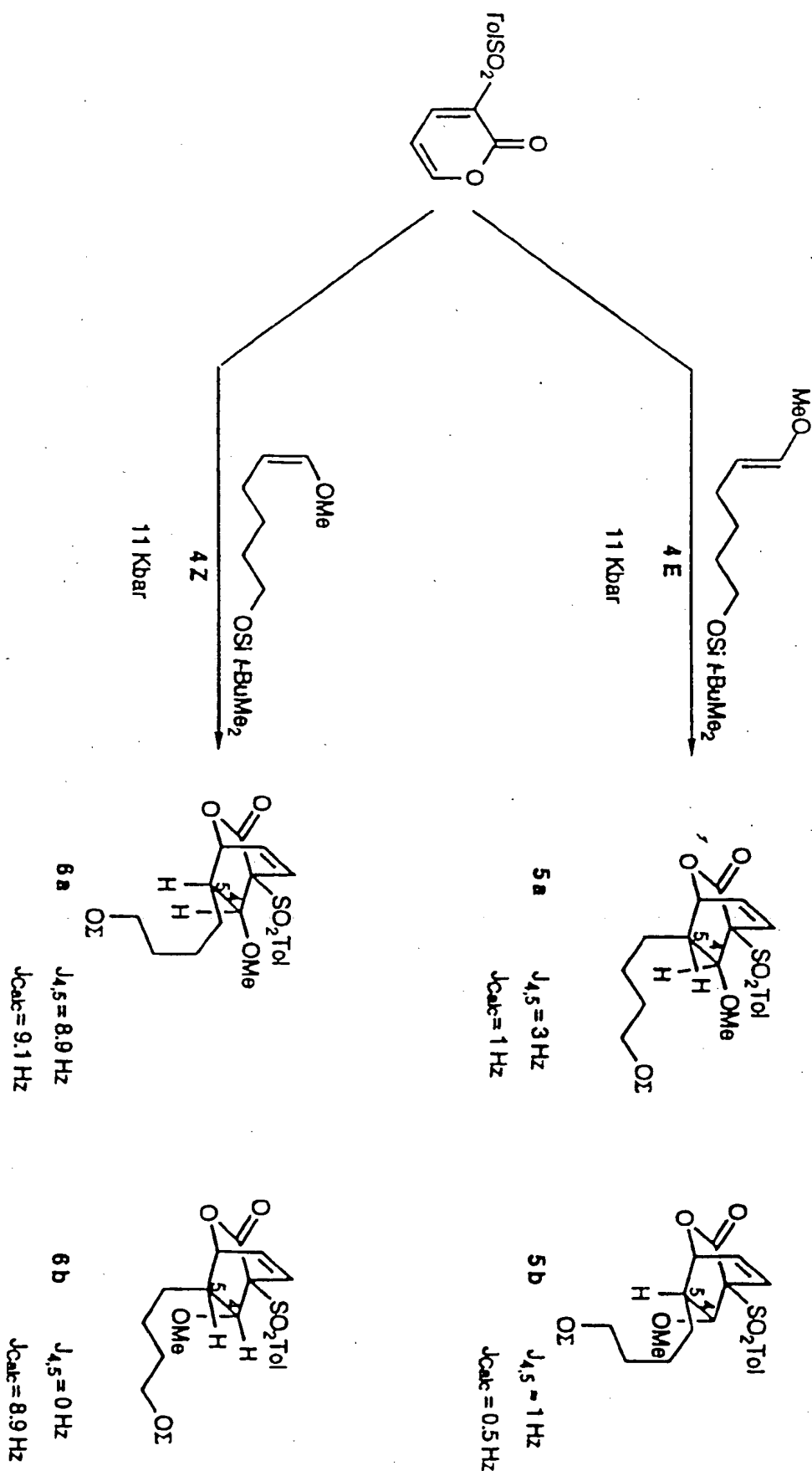
**DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED
EXEMPLARY EMBODIMENTS**

20 Uncatalyzed Diels-Alder cycloadditions between highly polarized dienes and dienophiles can occur step-wise rather than in the usual concerted fashion⁶. To probe this issue within the context of inverse-electron-demand Diels-Alder

25 cycloadditions using 2-pyrones substituted at the 3-position with highly electron-withdrawing (e.g.

3-sulfonyl, 3-acyl) substituents⁵, 3-p-toluenesulfonyl-2-pyrone and 1,2-disubstituted alkenes **4E** and separately **4Z** were placed under high pressure. In both of these electronically matched cases, the electron-poor 2-pyrone diene and the electron-rich vinylic ether cycloadded to produce isolable bicyclic lactone adducts without undesirable and often-encountered extrusion of CO₂ (Scheme I)

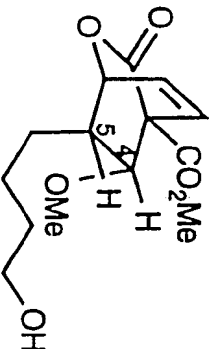
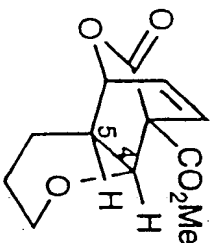
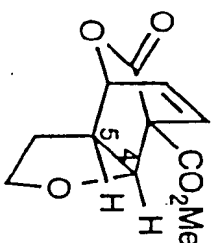
The most important aspect of these Diels-Alder reactions from a mechanistic viewpoint is that the cycloadducts retained the stereochemical information in the reactant vinylic ethers: dienophile **4E** led exclusively to trans-4,5-oriented products **5a** and **5b**, whereas dienophile **4Z** led exclusively to cis-4,5-oriented products **6a** and **6b**. Therefore, these polarized 2+4-cycloadditions must occur in a concerted rather than in a step-wise fashion⁶. The assignments of the 4,5-positional relationships were based on extensive precedent⁵, and the assignments of the 4,5-stereochemical relationships were based on the match of the 400 MHz ¹H NMR J_{4,5} coupling constants with those calculated using the Karplus equation for energy-minimized structures generated using Chem-3D (Scheme I)⁷. Bicyclic lactone **6a**, the very major cycloadduct, differed in a characteristic way⁵ from bicyclic lactone **6b** in terms of the

SCHEME I

chemical shift of the bridgehead hydrogen atom (δ 4.98 vs. 5.04) and the chemical shift of the C₄ hydrogen atom (δ 4.55 vs. 3.83). Also, irradiation of the C₅ hydrogen atom of lactone **6a** caused an 11 % nOe on the C₄ hydrogen atom. The large discrepancy between the observed and the calculated J_{4,5} coupling constant for cis-4.5-disubstituted bicyclic adduct **6b** was of considerable concern. Therefore, a series of similar cis-4.5-disubstituted bicyclic lactones was prepared. Examination of their J_{4,5} coupling constants (Table I) showed a very subtle effect of the nature of the substituents on this magnitude of the vicinal coupling constant. For example, the cycloadduct derived from the 6-membered cyclic vinyl ether showed J_{4,5}=0 Hz (entry 2), whereas that derived from the 5-membered cyclic vinyl ether showed J_{4,5}=8.5 Hz (entry 3). Finally, based on literature analogies in which E-alkenes underwent 2+4-cycloadditions more easily than Z-alkenes^{6e-g}, we were surprised to find that vinylic ether geometric isomer **4Z** reacted considerably faster than isomer **4E** with 3-tolysulfonyl-2-pyrone. Whereas vinylic ether isomer **4Z** yielded almost exclusively the endo-cycloadduct **6a**, as expected from previous results⁵, vinylic ether isomer **4E** gave a 1:2 mixture of cycloadducts **5a:5b**.

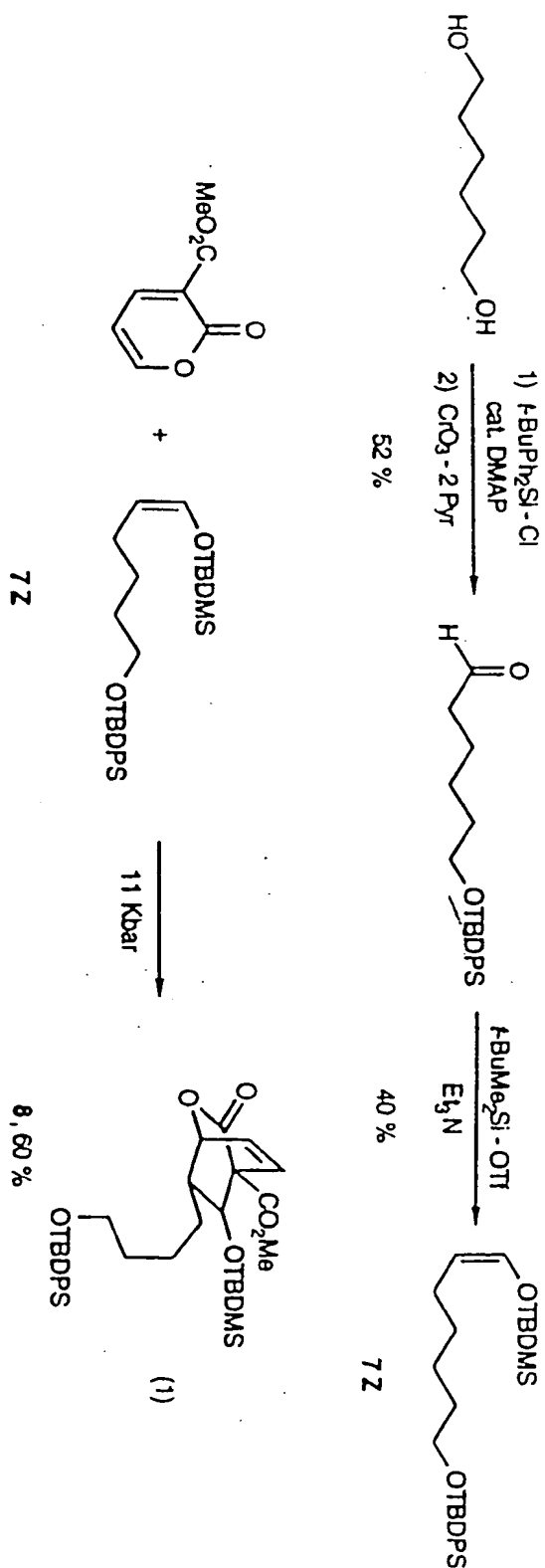
TABLE I

¹H NMR Data for Several *cis*-4,5-Disubstituted Bicycloadducts

| <u>Entry</u> | <u>Compound</u> | <u>J_{4,5} (Hz)</u> |
|--------------|---|-----------------------------|
| 1 |  | 0 |
| 2 |  | 0 |
| 3 |  | 8.5 |

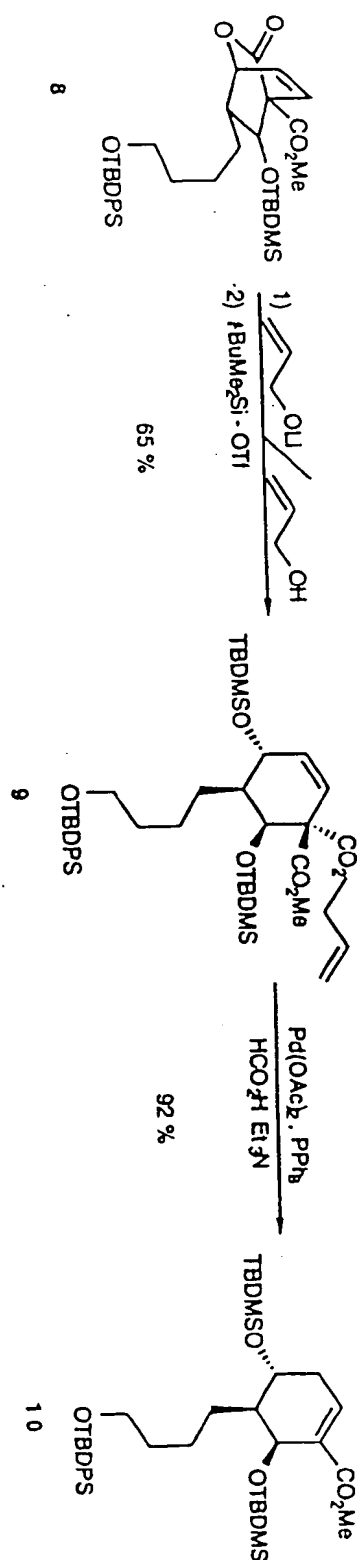
From a synthesis viewpoint, cycloadducts 5 and 6 turned out to be disappointing. Despite close structural similarity with other bridgehead-substituted toluenesulfonyl cycloadducts and related cyclohexene systems that underwent smooth reductive-desulfonylation⁸, we were unsuccessful using a variety of conditions (e.g., Al-Hg, Na-Hg, Raney nickel, Li/NH₃) to effect high-yielding reductive-desulfonylation. Also, it was anticipated that ultimate conversion of the methyl ether functionality into the desired alcohol group would be more difficult than deprotection of a silyl ether. Therefore, silylated vinylic ether 7Z, prepared according to literature precedent as illustrated in Scheme II⁹, and commercially available methyl 2-pyrone-3-carboxylate were subjected to high pressure cycloaddition (eq. 1).

Bicycloadduct 8 was the major product, isolated on gram scale in 60% yield, with the oxygen substituted at position-4, as expected based on the polar nature of the Diels-Alder cycloaddition and also on literature precedent⁵, with a cis-4,5-stereochemical relationship. This stereochemical outcome was expected based on the results in Scheme I with the 3-sulfonyl-2-pyrone and was confirmed by the observed large ¹H NMR J_{4,5} coupling constant (8.6 Hz)⁷ and by the characteristic chemical shifts of the bridgehead

SCHEME II

hydrogen atom at δ 5.1 and the C₄ hydrogen atom at δ 4.7. Also, irradiation of the C₅ hydrogen atom caused a 14% nOe on the C₄ hydrogen atom, confirming their cis-4,5-relationship. We have
5 not succeeded in preparing cleanly the isomeric silylated vinylic ether 7E for cycloaddition with methyl 2-pyrone-3-carboxylate.

Having served its chemical function of activating the pyrone diene (the unsubstituted
10 parent 2-pyrone is unreactive)^{5d,10} for cycloaddition with the electron-rich vinylic ether 7Z, the bridgehead carboxylate ester group in bicyclic lactone adduct 8 had to be removed. To complement our two-step lactone methanolysis and
15 high-pressure procedure for this type of decarboxylation¹¹, we report now a new and more convenience (i.e., not high pressure) two-step protocol (Scheme III). Although bicyclic lactone methyl ester 8 has two ester carbonyl groups, it
20 was gratifying to find that the lactone ring was chemospecifically attacked by lithium allyloxide to produce mixed methyl allyl malonate 9 in 75% yield. In accord with literature precedent¹², allyl ester 9 was smoothly decarboxylated using
25 palladium acetate; an unexpected but desired benefit of this procedure was conjugation of the cyclohexene double bond, giving the contiguously

SCHEME III

tetrasubstituted cyclohexene 10 in 92% yield
(Scheme III).

Without any surprises, highly functionalized
cyclohexene alcohol ester 10 was O-silylated and
5 then reduced to form allylic alcohol 11 (Scheme
IV). One flask Claisen rearrangement followed by
spontaneous thermal sulfoxide elimination was
achieved using our sulfinylated ortho ester
protocol¹³ giving an unusually favorable >10:1 Z:E
10 ratio of dienoate esters from which the desired Z-
dienoate 12 was isolated by chromatography in 80%
yield.

Established reactions as outlined in Scheme
IV below provided the crucial, fully O-protected,
15 racemic, A-ring phosphine oxide 13. Lythgoe-type
coupling¹⁴ of the conjugate base of phosphine oxide
13, generated using phenyllithium¹⁵, with C,D-ring
ketone 14 of natural absolute configuration
produced O-silylated derivatives of diastereomeric
20 2-(4'-hydroxylated) calcitriol analogues 3 and 3',
isolated in 50% yield.

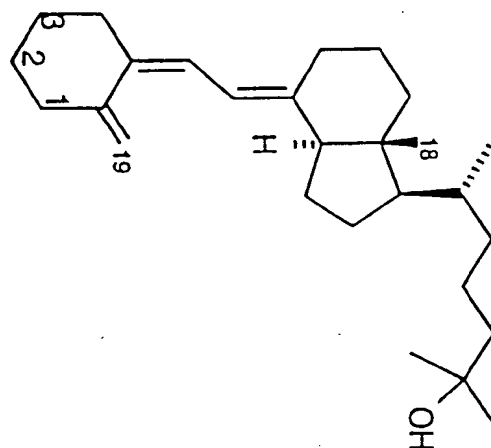
Fluoride-induced cleavage of the silyl
protecting groups proceeded easily at three of the
four silylated alcohol groups; desilylation at the
25 C₁ secondary alcohol position, however, was
unexpectedly slow, requiring considerably more
vigorous reaction conditions.

In another context¹⁶, we have observed that the C₁ secondary alcohol unit in calcitriol is chemically less reactive than the C₃ secondary alcohol toward esterifying reagents.

5 Nevertheless, fluoride-assisted quadruple desilylation under more vigorous conditions eventually yielded the desired calcitriol analogues 3 and 3'.

10 Easy HPLC separation gave each diastereomer in enantiomerically pure form. Tentative assignments of stereochemistry to diastereomers 3 and 3' were made by ¹H NMR in analogy with closely related calcitriol analogues; in diastereomeric pairs differing only by inversions of

15 stereochemistry at positions 1-3 but not in the C,D-ring or in the side chain, the 1 α -substituted diastereomer characteristically showed a lower field absorption for the C₁₈-methyl group and for one proton of the C₁₉-methylene group (Table II).

TABLE II.

¹H NMR
Chemical Shift
(δ)

| | 1 | 2 | 3 | C ₁₈ | C ₁₉ | Ref |
|----|--|--|--------------|-----------------|-----------------|------|
| | α -OH | α -OH | β -OH | 0.54 | 5.14 | 17 |
| | β -OH | β -OH | α -OH | 0.53 | 5.11 | 17 |
| | α -CH ₂ OH | - | β -OH | 0.54 | 5.02 | 15 |
| | β -CH ₂ OH | - | α -OH | 0.50 | 4.99 | 15 |
| | α -CH ₂ CH ₂ OH | - | β -OH | 0.54 | 4.90 | 13b |
| | β -CH ₂ CH ₂ OH | - | α -OH | 0.51 | 4.88 | 13b |
| 3 | 1 α -OH | 2 α -(CH ₂) ₄ OH | β -OH | 0.54 | 5.00 | this |
| 3' | 1 β -OH | 2 β -(CH ₂) ₄ OH | α -OH | 0.52 | 4.98 | work |

Thus, in only 11 steps from commercially available methyl 2-pyrone-3-carboxylate, two new vitamin D₃ analogues have been prepared, and the C,D-ring chiron 14 has been used to resolve
5 racemic A-ring phosphine oxide 13.

Preliminary biological evaluation of synthetic diastereomers 3 and 3' involved measuring their relative binding affinities to rat vitamin D binding protein (DBP) and also to the vitamin D receptor of bovine thymus (Table III). Diastereomer 3 had significantly higher affinity than ED-71 (1) for the vitamin D binding protein, but it had extremely low affinity for the vitamin D receptor; whether this separation of binding affinities has important mechanistic and/or medicinal value remains to be established. Diastereomer 3', on the other hand, had lower affinity than ED-71 (1) for the vitamin D binding protein, but it had higher affinity than ED-71 (1) for the vitamin D receptor. Determining the impact of these differences on possible use of these new analogues for chemotherapy of osteoporosis requires further biological testing.

TABLE III.

| RELATIVE BINDING AFFINITIES | | |
|---------------------------------------|------------|-------------------|
| | <u>DBP</u> | <u>D RECEPTOR</u> |
| 25(OH)-D ₃ | 90 | --- |
| 1,25(OH) ₂ -D ₃ | 1 | 1 |
| Ed-71(1) | 3.7 | 0.21 |
| 3 | 5.0 | 0.01 |
| 3' | 1.9 | 0.28 |

Relative binding affinities of diastereomers 3 and 3' to the vitamin D binding protein and to the vitamin D receptor showed some unusual trends. Diastereomer 3' surprisingly bound much more effectively to the vitamin D receptor than did the established osteoporosis drug candidate ED-71 (1).

EXAMPLES

General

Tetrahydrofuran and diethyl ether were distilled from benzophenone ketyl prior to use. Methylene chloride and triethylamine were distilled from calcium hydride immediately prior to use. Commercially available anhydrous solvents were used in other instances. All reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and unless otherwise specified were used as received without further purification. All reactions were run in flame-dried flasks under nitrogen unless otherwise specified. FT-IR spectra were determined using a Perkin-Elmer Model 1600 FT-IR spectrophotometer. The ^1H NMR were recorded on a Varian XL-400 spectrometer and Bruker AMX-300 spectrometer operating at 400 and 300 MHz, respectively. The ^{13}C spectra were recorded on the same instruments operating at 100 and 75 MHz, respectively. High resolution mass spectra were obtained on a two sector-high-

resolution VG-70S mass spectrometer run at 70 eV. A Leco Corp. Model No. PG-200-HPC 13 Kbar apparatus was used for the high-pressure studies.

Silylated Vinylic Ether 7Z

- 5 To a 100 mL round-bottomed flask containing 2.1 g (17.5 mmol) of 1,6-hexanediol, 2.7 mL (19.2 mmol) of triethylamine, and 10 mg of N,N-dimethylaminopyridine in 35 mL CH_2Cl_2 was added 5 mL (19.2 mmol) of t-butylchlorodiphenylsilane.
- 10 The reaction was stirred at room temperature for 12 h, or until complete by TLC. The reaction was quenched with 10 mL water, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 . The combined organic layers were dried
- 15 over MgSO_4 , filtered, and concentrated. The crude product was purified by column chromatography (10-20% EtOAc/Hexane) to afford 3.73 g (10.45 mmol, 60% yield) of the monosilated product as a clear oil.
- 20 To a 250 mL round-bottomed flask containing 10.14 mL (125.4 mmol) of pyridine in 50 mL of CH_2Cl_2 was slowly added 6.27 g (62.7 mmol) of chromium trioxide. The resultant deep burgundy solution was stirred for 15 minutes at room
- 25 temperature. At the end of this period, a solution of the above monosilated diol in 50 mL CH_2Cl_2 was added via cannula. A tarry, black

deposit separated immediately. This mixture was stirred for 1h at which time the CH_2Cl_2 was removed on a rotary evaporator and the tar was diluted with Et_2O . This heterogeneous mixture was filtered
5 through silica gel to give a yellow liquid which was concentrated. The crude product was purified by column chromatography (5% EtOAc/Hexane) to give 3.17 g (8.9 mmol, 85% yield) of the aldehyde as a clear oil. ^1H NMR (300 MHz, CDCl_3) δ 9.74 (s, 1H),
10 7.675 (m, 4H), 7.40 (m, 6H), 3.66 (t, $J=6.2$ Hz, 2H), 2.34 (m, 2H), 1.58 (m, 4H), 1.41 (m, 2H), 1.04 (s, 9H), IR (CHCl_3) 3013 cm^{-1} , 2931 cm^{-1} , 1713 cm^{-1} .

The above aldehyde was then diluted with 20
15 mL of benzene and 1.64 mL (11.75 mmol) of triethylamine. The resulting mixture was cooled to 0°C and 2.45 mL (10.68 mmol) of t-butyldimethylsilyl triflate was added. The reaction was allowed to warm to room temperature
20 and stirred for 1 h. The reaction was quenched with brine and diluted with Et_2O . The organic layer was separated, and the aqueous layer was washed with Et_2O . The combined organic layers were dried over MgSO_4 , filtered, and concentrated. The
25 crude product was purified by column chromatography (Hexane) or silica gel that was slurry-packed with 1% triethylamine/hexane. The silylated vinylic ether 7Z (1.67 g, 3.56 mmol, 40%

yield) was a clear oil; $R_f=0.8$ (25% EtOAc/Hexane);
 ^1H NMR (300 MHz, CDCl_3) δ 7.65 (m, 4H), 7.41 (m,
6H), 6.17 (dt, $J=5.9, 1.5$ Hz, 1H), 4.43 (dd,
 $J=7.4, 5.9$ Hz, 1H), 3.61 (t, $J=6.6$ Hz, 2H), 2.09
5 (ddt, $J=14.7, 7.4, 1.5$ Hz, 2H), 1.54 (m, 2H), 1.37
(m, 2H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75
MHz, CDCl_3) δ 138.50, 135.54 (4), 134.15 (2),
129.50, 129.43, 127.55 (2), 127.53, 110.54, 63.93,
32.31, 26.87 (3), 25.99 (3), 25.80, 25.66, 23.36,
10 19.22, -2.92, -5.36; IR (CHCl_3) 3013, 2931, 1654,
1108 cm^{-1} ; HRMS m/e calcd. for $\text{C}_{24}\text{H}_{35}\text{O}_2\text{Si}_2$ 411.2176,
found 411.2179.

Cycloadduct 8

A 12 cm piece of 3/8" heat shrinkable teflon
15 tubing (Ace Glass cat. #12685-40) was sealed on
one end with a glass dowel plug by using a heat
gun. To this 500.0 mg (3.24 mmol) of methyl 2-
pyrone-3-carboxylate (Aldrich), 2g (4.26 mmol) of
silylated vinylic ether 7Z, 10 mg of barium
20 carbonate, and 2 mL of dry CH_2Cl_2 was added. The
open end of tubing was then sealed in a similar
fashion with a second glass dowel plug. This
'sealed tube' was then pressurized at 10-11 Kbar at
room temperature for 4 days. The reaction mixture
25 was concentrated on a rotary evaporator and the
residue was purified by column chromatography (5%
EtOAc/Hexane) to give 1.21 g (1.94 mmol, 60%) of

the cycloadduct **8** as a clear oil; $R_f=0.58$ (25% EtOAc/Hexane); ^1H NMR (300 MHz, CDCl_3) δ 7.65 (m, 4H), 7.41 (m, 6H), 6.78 (dd, $J=7.8$, 2.8 Hz, 1H), 6.46 (dd, $J=7.8$, 5.1 Hz, 1H), 5.09 (ddd, $J=5.1$, 3.8, 1.0 Hz, 1H), 4.71 (dd, $J=7.6$, 1.00 Hz, 1H), 3.89 (s, 1H), 3.66 (t, $J=6.1$ Hz, 3H), 2.35 (ddd, $J=7.6$, 3.8, 2.8 Hz, 1H), 1.56 (m, 2H), 1.26 (m, 2H), 1.06 (s, 9H), 0.91 (m, 2H), 0.78 (s, 9H), 0.012 (s, 3H), 0.006 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.93, 167.51, 135.51 (4), 133.70 (2), 130.46, 129.53 (2), 128.64, 127.54 (4), 76.12, 69.36, 63.12, 52.7, 44.72, 32.37, 27.09, 26.75 (3), 25.64 (3), 25.56, 25.31, 23.34, 19.09, 18.04, -3.90, -5.03, IR (CHCl_3) 1760, 1743 cm^{-1} ; HRMS m/e calcd. for $\text{C}_{31}\text{H}_{41}\text{O}_6\text{Si}_2$ 565.2442, found 565.2450.

Mixed Malonate **9**

To a 25 mL round-bottomed flask with 500 mg (0.80 mmol) of cycloadduct **8** and 2 mL of CH_2Cl_2 at 0°C was added dropwise, via syringe, 962 μL of a freshly made 1.0 M solution of lithium allyloxide in allyl alcohol. The reaction mixture was allowed to warm to room temperature after the addition. Reaction was complete by TLC after 2 hours. The mixture was quenched with 2 mL aq. NH_4Cl and extracted with CH_2Cl_2 . The organic layer was dried with MgSO_4 , filtered, and concentrated on a rotary evaporator. The residue was purified by

column chromatography (0-20% EtOAc/Hexane) to give 410 mg (0.60 mmol, 75%) of the desired malonate as a clear oil; R_f =0.42 (25% EtOAc/Hexane); ^1H NMR (300 MHz, CDCl_3) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.96 (s, 2H), 5.83 (ddt, J =17.2, 10.5, 5.6 Hz, 1H), 5.36 (dd, J =17.2, 1.5 Hz, 1H), 5.22 (dd, J =10.5, 1.5 Hz, 1H), 4.76 (s, 1H), 4.63 (ddt, J =13.3, 5.6, 1.4 Hz, 1H), 4.51 (ddt, J =13.3, 5.6, 1.4 Hz, 1H), 4.02 (t, J =8.6 Hz, 1H), 3.74 (s, 3H), 3.69 (t, J =6.1 Hz, 2H), 1.71 (m, 2H), 1.64 (m, 2H), 1.57 (s, 1H), 1.28 (m, 2H), 1.05 (s, 9H), 0.81 (s, 9H), 0.07 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.11, 167.95, 135.41 (4), 134.07 (2), 133.89, 131.17, 129.34 (2), 127.44 (4), 122.47, 118.43, 71.70, 68.64, 65.72, 63.89, 61.38, 52.57, 46.04, 32.45, 26.76 (3), 25.94 (3), 23.25, 19.04, 18.27, 14.02, -3.79, -4.44; IR (CHCl_3) 1737 cm^{-1} ; HRMS m/e calcd. for $\text{C}_{34}\text{H}_{47}\text{O}_7\text{Si}_2$ 623.2860, found 623.2865.

To a 25 mL round-bottomed flask with 380 mg (0.56 mmol) of the allyl ester alcohol, 78 μL (0.67 mmol) of 2,6-lutidine, and 1.5 mL of CH_2Cl_2 at 0°C was added 154 μL (0.67 mmol) of *t*-butyldimethylsilyl trifluoroethanesulfonate dropwise via syringe. The reaction was complete by TLC after 10 minutes. The reaction was quenched at 0°C with 1 mL water and allowed to warm to room temperature. Extraction with CH_2Cl_2

followed by drying with MgSO_4 , filtration, and concentration afforded a viscous oil which was purified by column chromatography (5% EtOAc/Hexane) giving 390 mg (0.49 mmol, 87%) of O-silylated mixed malonate 9 as a clear oil; $R_f=0.6$ (25% EtOAc/Hexane); ^1H NMR (300 MHz, CDCl_3) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.87 (d, $J=2.68$ Hz, 2H), 5.83 (ddt, $J=17.2, 10.5, 5.6$ Hz, 1H), 5.36 (dd, $J=17.2, 1.5$ Hz, 1H), 5.22 (dd, $J=10.5, 1.5$ Hz, 1H), 4.76 (s, 1H), 4.63 (ddt, $J=13.3, 5.6, 1.4$ Hz, 1H), 4.51 (ddt, $J=13.3, 5.6, 1.4$ Hz, 1H), 4.13 (d, $J=9.2$ Hz, 1H), 3.74 (s, 3H), 3.69 (t, $J=6.1$ Hz, 2H), 1.76 (m, 2H), 1.61 (m, 2H), 1.55 (s, 1H), 1.28 (m, 2H), 1.06 (s, 9H), 0.88 (s, 9H), 0.83 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), - 0.06 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.27, 167.96, 135.45 (4), 133.99 (2), 133.97, 131.33, 129.38 (2), 127.48 (4), 121.83, 118.43, 71.70, 69.16, 65.69, 64.00, 61.47, 52.52, 46.10, 32.67, 26.81 (3), 25.99 (3), 25.80 (3), 23.25, 19.10, 18.35, 17.99, 14.11, -3.83, -4.20, -4.34, -4.70; IR (CHCl_3) 1737 cm^{-1} ; HRMS m/e calcd. for $\text{C}_{40}\text{H}_{61}\text{O}_7\text{Si}_3$ 737.3725, found 737.33730.

Cyclohexene Ester 10

A mixture of 380 mg (0.48 mmol) of malonate 9, 23 μL (0.60 mmol) formic acid, 87 μL (0.62 mmol) triethylamine, 10 mg (0.04 mmol)

triphenylphosphine, and 2 mg (0.01 mmol) palladium acetate in 1.5 mL dioxane was sealed in a 5 mL hydrolysis tube and heated at 100°C for 12 h. After evaporation of dioxane, 1 N HCl (1mL) was
5 added, and the mixture was extracted with CH₂Cl₂ (2 mL x 2). The organic solution was washed with saturated NaHCO₃ and dried over MgSO₄, filtered, and concentrated. The oily residue was purified by column chromatography (0-10% EtOAc/Hexane) to
10 give 310 mg (0.44 mmol, 92%) of cyclohexene ester 10 as a clear oil: R_f=0.50 (25% EtOAc/Hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.68 (m, 4H), 7.41 (m, 6H), 6.87 (t, J=1.5 Hz, 1H), 5.76 (s, 1H), 4.72 (s, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 3.74 (s, 3H),
15 3.69 (t, J=6.1 Hz, 2H), 2.60 (dt, J=14.3, 5.6 Hz, 1H), 2.10 (ddd, J=16.9, 8.4, 1.5 Hz, 1H), 1.58 (m, 2H), 1.55 (s, 1H), 1.38 (m, 2H), 1.26 (m, 2H), 1.05 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), -0.07 (s, 3H), -0.09 (s, 3H);
20 ¹³C NMR (75 MHz, CDCl₃) δ 167.01, 135.51 (4), 134.05 (2), 133.16, 132.35, 129.45 (2), 127.55 (4), 66.89, 64.16, 51.50, 47.43, 33.1, 26.87, 25.95, 25.92, 25.89, 25.84, 25.68, 23.31, 19.17, 18.42, 18.06, -4.09, -4.37, -4.74, -5.39; IR
25 (CHCl₃) 1713 cm⁻¹; HRMS m/e calcd. for C₃₆H₅₇O₅Si₃ 653.3514, found 653.3516.

Allylic Alcohol 11

To a 25 mL round-bottomed flask containing 695 mg (0.98 mmol) of cyclohexene ester 10 in 8 mL toluene at -78°C was added 2.15 ml (2.15 mmol) of 1 M diisobutylaluminum hydride in toluene dropwise via syringe. The reaction was complete by TLC after 1h. The reaction was quenched by addition at -78°C of 5 mL of 2 M potassium sodium tartrate followed by dilution with 10 mL EtOAc. After the mixture was allowed to warm to room temperature and stirred for 0.5 h, two layers were visible. These were separated and the aqueous layer was washed with EtOAc. The combined organic fractions were washed with water, and brine, and dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (0-25% EtOAc/Hexane) to give 518 mg (0.76 mmol, 77%) of allylic alcohol 11 as a clear oil: R_f=0.35 (25% EtOAc/Hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.51 (t, J=1.5 Hz, 1H), 4.80 (s, 1H), 4.22 (d, J=12.0 Hz, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 3.74 (s, 3H), 3.69 (t, J=6.1 Hz, 2H), 2.60 (dt, J=14.3, 5.6 Hz, 1H), 2.10 (ddd, J=16.9, 8.4, 1.5 Hz, 1H), 1.58 (m, 2H), 1.55 (s, 1H), 1.38 (m, 2H), 1.26 (m, 2H), 1.05 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H), -0.07 (s, 3H), -0.09 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 137.81, 135.51 (4), 134.04 (2),

129.47 (2), 127.55 (4), 122.65, 70.03, 68.32,
65.68, 63.77, 46.36, 33.11, 31.28, 26.85 (3),
25.90 (3), 25.82 (3), 25.51, 25.43, 24.52, 24.03,
19.21, 18.06, -4.20, -4.82 (2), -4.92; IR (CHCl₃)
5 3401, 1713 cm⁻¹; HRMS m/e calcd. for C₃₄H₅₇O₄Si₃
625.3565, found 625.3570.

Z-Dienoate 12

To 510 mg (0.75 mmol) of allylic alcohol 11
in a sealable hydrolysis tube was added 642 mg
10 (2.2 mmol) triethylphenyl sulfinyl orthoacetate
and 1.0 mg 2,4,6-trimethylbenzoic acid and 2 mL
CH₂Cl₂. The tube was purged with argon and sealed,
then heated at 100°C for 12h. The reaction
mixture was concentrated. Crude ¹H NMR showed a
15 >10:1 mixture of Z:E isomers. The crude product
was purified via PTLC (10% EtOAc/Hexane) to give
450 mg (0.60 mmol, 80%) of Z dienoate 12 as a
clear oil; R_f=0.61 (25% EtOAc/Hexane); ¹H NMR (400
MHz, CDCl₃) δ 7.68 (m, 4H), 7.41 (m, 6H), 5.61 (s,
20 1H), 5.17 (t, J=1.8 Hz, 1H), 5.09 (t, J=1.3 Hz,
1H) 4.55 (dd, J=5.5, 1.3 Hz, 2H), 4.12 (q, J=7.2
Hz, 2H), 3.97 (t, J=3.8 Hz, 1H), 3.66 (t, J=6.1
Hz, 2H), 2.48 (dd, J=5.5, 1.4 Hz, 1H), 2.15 (dd,
J=3.8, 1.7 Hz, 1H), 1.70 (m, 1H), 1.58 (m, 2H),
25 1.55 (s, 1H), 1.38 (m, 2H), 1.26 (m, 2H), 1.04 (s,
9H), 0.87 (s, 18H), 0.05 (s, 6H), 0.04 (s, 6H); ¹³C
NMR (75 MHz, CDCl₃) δ 165.92, 157.09, 153.29,

145.39, 135.52 (4), 134.09 (2), 129.47 (2), 127.55
(4), 117.17, 70.23, 63.91, 59.67, 50.54, 32.98,
26.86 (3), 25.80 (3), 25.74 (3), 19.20, 18.18,
17.98, 14.30, 14.13, -4.66, -4.83, -4.87, -5.17;
5 IR (CHCl₃) 3025, 2931, 1713 cm⁻¹; HRMS m/e calcd.
for C₄₃H₇₀O₅Si₃ 750.4531, found 750.4538.

Phosphine Oxide 13

To a 25 mL round-bottomed flask containing
180 mg (0.24 mmol) of dienoate 12 in 2 mL toluene
10 at -78°C was added dropwise 530 µL (0.53 mmol) of
a 1 M solution of diisobutylaluminum hydride via
syringe. After 1h the reaction was complete by
TLC. The reaction was quenched at -78°C by
addition of 2 mL of 2 N potassium sodium tartrate
15 and dilution with 5 mL EtOAc. The mixture was
allowed to warm to room temperature and stirred
0.5 h until two distinct phases appeared. The
organic phase was separated, and the aqueous phase
was washed with EtOAc. The combined organic
20 extracts were washed with water and brine, dried
over MgSO₄, filtered, and concentrated. The crude
mixture was quickly purified by column
chromatography (10-20% EtOAc/Hexane) to give 167
mg (0.24 mmol) of the desired allylic alcohol.

25 To a 10 mL round-bottomed flask containing
152 mg (1.14 mmol) N-chlorosuccinimide in 3 mL
CH₂Cl₂ at 0°C was added 90 mL (1.22 mmol) of

dimethyl sulfide via syringe. A white precipitate formed immediately upon addition. This mixture was cooled to -20°C and stirred for 20 minutes. The above allylic alcohol in 2 mL CH_2Cl_2 was then added
5 to the heterogeneous mixture via cannula. The reaction was stirred for 0.5 h at -20°C and then allowed to warm to room temperature and stirred for an additional 1 h. The organic layer was washed with water, brine, dried with MgSO_4 ,
10 filtered, and concentrated. The crude product was passed through florisil (5% EtOAc/Hexane) to afford 154 mg (0.21 mmol) of the desired allylic chloride as a yellow oil.

To a 10 mL round-bottomed flask containing
15 the above allylic chloride in 2 mL THF at -78°C was added dropwise via cannula a 0.5 M solution of potassium diphenylphosphide in THF. The addition was stopped once the red color persisted. After 1 h the reaction was allowed to slowly warm to 0°C
20 at which point it was complete by TLC. The reaction was quenched with 2 drops of water and the THF was removed. The residue was diluted with 2 mL CH_2Cl_2 and 10 drops of 30% H_2O_2 was added. After 1 h the reaction was diluted with CH_2Cl_2 and
25 water and the layers were separated. The organic phase was concentrated. The crude product was purified by column chromatography (25-50% EtOAc/Hexane) to give 121 mg (0.13 mmol, 54% from

Z-dienoate 12) of the phosphine oxide 13 as a clear oil: $R_f=0.56$ (75% EtOAc/Hexane); ^1H NMR (400 MHz, CDCl_3) δ 7.74-7.36 (m, 20H), 5.3 (dd, $J=15.1$ Hz, 6.6H), 5.11 (s, 1H), 4.75 (s, 1H), 4.42 (d, $J=3.2$ Hz, 1H), 3.87 (dd, $J=8.9, 4.9$ Hz, 1H), 3.65 (t, $J=6.6$ Hz, 3H), 3.40 (dt, $J=15.1, 8.9$ Hz, 1H), 3.14 (dt, $J=16.0, 6.7$ Hz, 1H), 2.4 (dd, $J=13.3, 3.2$ Hz, 1H), 2.06 (dd, $J=14.2, 2.9$ Hz, 1H), 1.56 (m, 1H), 1.53 (m, 2H), 1.43 (m, 2H), 1.35 (m, 2H), 1.04 (s, 9H), 0.88 (s, 9H), 0.82 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H), -0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 146.20 (2), 141.17, 135.50 (4), 134.06 (2), 131.71, 131.04, 130.92 (4), 129.45 (2), 128.63 (4), 128.47 (2), 127.53 (4), 114.39, 70.15, 63.90, 50.72, 32.97, 30.09, 26.83 (3), 25.79 (3), 25.05, 24.06, 19.18, 18.04, -4.58, -4.69, -4.89, -5.07; IR (CHCl_3) 3025, 2954, 1472, 1255 cm^{-1} ; HRMS m/e calcd. for $\text{C}_{49}\text{H}_{68}\text{O}_4\text{Si}_3$ 835.4163, found 835.4169.

20 Calcitriol Analogues 3 and 3'

To a 10 mL round-bottomed flask containing 95 mg (0.103 mmol) of phosphine oxide 13 in 1.4 mL of THF at -78°C was added dropwise 67 μL (0.103 mmol) of a 1.54 M solution of phenyllithium in THF. The resultant red solution was allowed to stir for 10 minutes. A solution of 20 mg (0.056 mmol) of C-D ring 14 in 1 mL of THF was added via cannula. The

reaction was complete after 1 h by TLC following disappearance of C-D ring. The reaction was quenched by addition of 1 mL 1:1 KHCO_3 /2 N potassium sodium tartrate. The layers were separated and the organic phase was washed with brine, dried over MgSO_4 , filtered and concentrated. The crude product was rapidly purified by filtration through silica gel using 50% EtOAc/Hexane as solvent to give 47 mg (0.052 mmol, 50% yield) of the coupled product. The silyl ethers were cleaved by redissolving the product in 1 mL of THF and treating with 220 μL (0.22 mmol) of tetrabutylammonium fluoride. After 24 h the reaction was diluted with water and the layers were separated, dried over MgSO_4 , filtered and concentrated. The diastereomers were separated and purified by reverse phase HPLC (30-20% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ on a C-18 semi-prep. column) to afford 1.1 mg (0.002 mmol, 4% yield) of analogue 3, and 4.4 mg (0.008 mmol, 16% yield) of analogue 3', both as white solids. ^1H NMR of 3 (300 MHz, CDCl_3) δ 6.41 (d, $J=11.6$ Hz, 1H), 6.02 (d, $J=11.6$ Hz, 1H), 5.29 (s, 1H), 5.02 (s, 1H), 4.35 (s, 1H), 3.82 (m, 1H), 3.68 (t, $J=6.1$ Hz, 2H), 2.78 (d, $J=11.5$ Hz, 1H), 2.62 (dd, $J=11.5$, 3.5 Hz, 1H), 2.20 (dd, $J=10.2$, 3.5 Hz, 1H), 1.98 (m, 2H), 1.68-1.20 (m), 0.92 (s, 3H), 0.90 (s, 3H), 0.54 (s, 3H). ^1H NMR of 3' (300 MHz, CDCl_3) δ 6.40 (d,

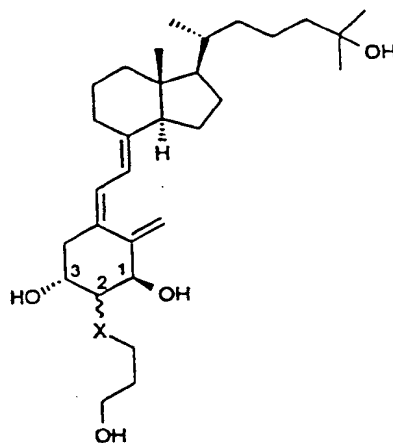
J=11.6 Hz, 1H), 5.98 (d, J=11.6 Hz, 1H), 5.27 (s, 1H), 4.98 (s, 1H), 4.38 (s, 1H), 3.87 (m, 1H), 3.68 (t, J=6.1 Hz, 2H), 2.82 (d, J=11.5 Hz, 1H), 2.65 (dd, J=11.5, 3.5 Hz, 1H), 2.24 (dd, J=10.2, 3.5 Hz, 1H), 1.68-1.20 (m), 0.92 (s, 3H), 0.90 (s, 3H), 0.52 (s, 3H); UV-Vis (MeOH) λ_{max} 268 nm (ϵ 15,600); HRMS m/e calcd. for $\text{C}_{31}\text{H}_{50}\text{O}_3$ 470.3760, found 470.3771.

2-Fluorides

10 The above-described methods for producing the vitamin D₃ analogues with alcohols substituted in the 2-position can be readily modified to produce comparable analogues with fluorides substituted in the two position (18-21). Table IV lists the
15 fluoride analogues of the present invention.

TABLE IV

2-SUBSTITUTED FLUORIDES OF CALCITRIOL



Position

| <u>3</u> | <u>2</u> | <u>1</u> |
|------------|---|------------|
| 3 β | 2 α -(CH ₂) ₄ F | 1 α |
| 3 α | 2 β -(CH ₂) ₄ F | 1 β |
| 3 β | 2 α -(CH ₂) ₃ F | 1 α |
| 3 α | 2 β -(CH ₂) ₃ F | 1 β |

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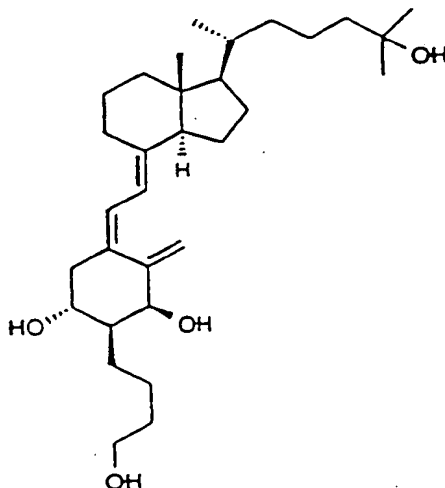
20 While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiments, it is to be understood that the invention is not to be limited to the disclosed embodiments, but on
25 the contrary is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

WHAT IS CLAIMED IS:

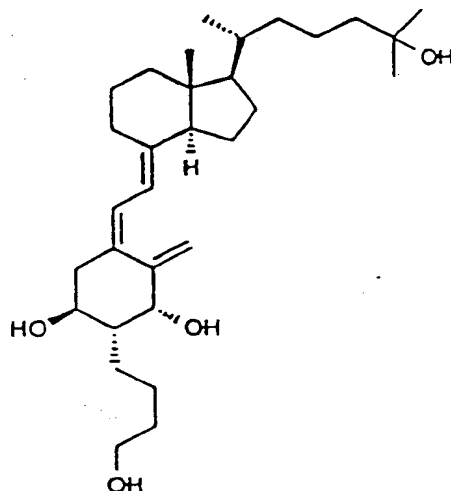
1. A vitamin D₃ analogue which includes a substituent in the 2-position selected from the group consisting of alcohols and fluorides.

5 2. The analogue of claim 1 wherein said substituent is $-(CH_2)_4OH$.

3. The analogue of claim 2 having the following structural formula:



4. The analogue of claim 2 having the following structural formula:



5. The analogue of claim 1 wherein said substituent is $-(CH_2)_3F$.

5 6. The analogue of claim 1 wherein said substituent is $-(CH_2)_4F$.

7. A method for the preparation of a vitamin D_3 analogue which includes an alcohol substituent in the 2-position, comprising the steps of:

10 a) subjecting methyl 2-pyrone-3-carboxylate and a silylated vinylic ether to high pressure cycloaddition to form a bicycloadduct;

 b) reacting the bicycloadduct with lithium allyloxide to produce a mixed methyl allyl malonate;

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- c) decarboxylating the mixed methyl allyl malonate with palladium acetate to yield a cyclohexene ester;
- d) silylating and reducing the cyclohexene ester to form an alcohol;
- e) subjecting the allylic alcohol to a Claisen rearrangement followed by spontaneous thermal sulfoxide elimination to form a Z-dienoate;
- f) reacting the Z-dienoate with a hydride to form an allylic alcohol;
- g) reacting the allylic alcohol with N-chlorosuccinimide and dimethyl sulfide to form an allylic chloride;
- h) reacting the allylic chloride with diphenylphosphide and then with hydrogen peroxide to form a phosphine oxide;
- i) reacting the phosphine oxide with phenyllithium to produce a conjugate base of the phosphine oxide;
- j) coupling the conjugate base of phosphine oxide with a C,D-ring ketone to produce O-silylated derivatives of diastereomeric 2-(4'-hydroxylated) calcitriol analogues; and
- k) separating and isolating the analogues.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/07595

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 401/00

US CL :552/653

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 552/653; C07C 401/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|--------------|---|-------------------------|
| P, Y | US, A, 5,389,622 (POSNER ET AL.) 14 February 1995, see entire document. | 1-4 |
| X -- Y | JP, A, 6-41059 (NAKASOTO SEIYAKU KK) 15 February 1994, see entire document. | 1, 2, 4 ----- 1-6 |
| P, X | JOURNAL OF ORGANIC CHEMISTRY, VOLUME 59, NUMBER 25, ISSUED 16 DECEMBER 1994, POSNER ET AL., "STEREOCONTROLLED TOTAL SYNTHESIS OF CALCITRIOL DERIVATIVES: 1,25-DIHYDROXY-2-(4'-HYDROXYBUTYL) VITAMIN D ANALOGS OF AN OSTEOPOROSIS DRUG, PAGES 7855-7861. | 1-4 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" document defining the general state of the art which is not considered to be part of particular relevance | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" earlier document published on or after the international filing date | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" document member of the same patent family |
| "O" document referring to an oral disclosure, use, exhibition or other means | |
| "P" document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

18 JUNE 1995

Date of mailing of the international search report

29 SEP1995

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